UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/373,938	08/13/1999	PAUL HALLENBECK		3124

1095 7590 04/02/2003

THOMAS HOXIE
NOVARTIS, CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 430/2
EAST HANOVER, NJ 07936-1080

EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/373,938	Hollenbeck et al.
Examiner	**Art Unit**
Joseph Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be availeble under the provisions of 37 CFR 1.136 (e). In no event, however, may e reply be timely filed after SIX (6) MONTHS from the meiling date of this communication.
- If the period for reply specified ebove is less than thirty (30) days, e reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified ebove, the meximum stetutory period will epply end will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by stetute, ceuse the epplication to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later then three months after the mailing dete of this communication, even if timely filed, may reduce eny earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 16, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 28-31, and 33-49* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 28-31, and 33-49* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Nov 26, 2002* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Petent Drewing Review (PTO-948)
3) ☐ Infomretion Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summery (PTO-413) Peper No(s). _____
5) ☐ Notice of Informel Patent Application (PTO-152)
6) ☐ Other:

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on December 16, 2002, paper number 22, has been entered.

DETAILED ACTION

This is an original application filed August 13, 1999.

As requested in Applicants request for continued examination the after final amendment filed November 22, 2002, paper number 19, has been entered. The specification has been amended. Claims 4-27 and 32 have been canceled. Claims 1, 2, 28 and 33 have been amended. Claims 34-49 have been added. Claims 1-3, 28-31, 33-49 are pending and currently under examination.

Specification

As noted in the advisory action, Applicants' response to the sequence compliance requirements has satisfied the requirements of 37 CFR 1.821 through 1.825.

Drawings

The corrected or substitute drawings were received on November 22, 2002. The drawings have been entered and are found acceptable by Examiner for review.

Response to Amendment

The declaration filed on November 26, 2002, paper number 18, under 37 CFR 1.131 is sufficient to overcome the 35 U.S.C. 102 and 103 rejections rejection over the Leboulch *et al.* reference (published June 3, 1999). Applicants declaration that the instant invention was conceived and reduced to practice prior to the publication date of Leboulch *et al.* has antedated the Leboulch *et al.* reference.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 43 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, independent claim 1 is directed to a adenoviral vector which is a polynucleotide, however dependent claims 43 and 44 recite SEQ ID NOs: 2 and 5 which are amino acid sequences. The claims are unclear and confusing because an amino acid sequence can not be comprised in a polynucleotide vector. Amending the claims to be directed to the

appropriate polynucleotide sequences or indicating the polynucleotide sequences encode the amino acid sequences would obviate the basis of the rejection.

Claim 42 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 42 is drawn to using the leader sequence of BM40, however the sequence considered to be the leader sequence is not set forth nor specifically defined in the specification.

Claim 45 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the metes and bounds encompassed by the recitation of 'at least the majority of' is indefinite. It is noted the specification provides literal support for this amendment, however the specification does not specifically define what is encompassed by the term 'a majority' and it is unclear how much sequence must be deleted to be considered a majority or how little could be left and still not be considered a majority to have been removed.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an

> application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 28, 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Crystal *et al.* (US2002/0076395 A1).

Crystal *et al.* teach methods and materials for treating adipose tissue with anti-angiogenic factors. More specifically, Crystal *et al.* teach that adenoviral vectors are capable and can be used for expressing the anti-angiogenic factor endostatin (see claims 1, 3-8). Demonstrating the ability of an adenoviral vector to express an anti-angiogenic protein, Crystal *et al.* provide a working example of the transfection of mammalian cells in rat adipose tissue (see figures 1-4).

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1, 28, 29, 34-37, 39, 40, 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman *et al.* (WO 96/35774) and O'Reilly *et al.* (US Patent 5,854,205).

At the time of filing, O'Reilly *et al.* teach anti-angiogenic compositions and methods of use. Specifically, O'Reilly *et al.* teach endostatin sequences derived from the N-terminus of collagen XVIII (see figure 5 and column 2, lines 20-24). O'Reilly *et al.* teach that administration of endostatin to human and animal tumors prevents growth and expansion of the tumor (column 2, lines 31-42). By example, O'Reilly *et al.* teach that administration of both mouse and human endostatins are capable of preventing tumor growth in an animal model (see figure 11). O'Reilly *et al.* demonstrate that various vectors can be used to produce endostatin and the protein produced is effective *in vivo* for reducing tumor size (see for example EXAMPLE 5). Further, O'Reilly *et al.* teach that nucleic acid sequences encoding endostatin can be used in and administered by other methodologies such as gene therapy (column 9, lines 35-37). While O'Reilly *et al.* teaches that the nucleic acid sequences encoding endostatin can be used in gene therapy protocols, they do not provide the specific methodology for the delivery of endostatin. Similar to O'Reilly *et al.*, Folkman *et al.* teach that administration of anti-angiogenic proteins, also termed angiostatin proteins or endothelial proliferation inhibitor proteins, are effective in preventing angiogenesis and useful in methods of treating and inhibiting angiogenesis of tumors

(see abstract and examples provided on pages 2-5). Further, Folkman *et al.* teach that the anti-angiogenic proteins can be delivered by a variety of means and methods, including the use of adenoviral vectors in gene therapy protocols (pages 23-24 and 26). Both O'Reilly *et al.* and Folkman *et al.* teach that human endothelial cells present in a blood vessel are affected by the anti-angiogenic protein and providing an anti-angiogenic protein to cells prevent angiogenesis (O'Reilly *et al.* figures 8 and 12 and column 2 lines 31-42 and Folkman *et al.* pages 4-5 and 35). Finally, both O'Reilly *et al.* and Folkman *et al.* provide expression of the anti-angiogenic proteins by expression vectors which use promoters other than the endogenous anti-angiogenic promoter. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the adenoviral delivery methods for the delivery of anti-angiogenic factors disclosed by Folkman *et al.* for the delivery of the specific anti-angiogenic protein endostatin disclosed by O'Reilly *et al.* One having ordinary skill in the art would have been motivated to use an adenoviral vector for the delivery of the anti-angiogenic protein endostatin because adenoviral vectors 'are capable of transducing novel genetic sequences into target cells *in vivo*', 'have high efficiencies of infectivity' and provide high long term levels of expression of the gene of interest (Folkman *et al.* page 24, lines 5-15). There would have been a reasonable expectation of success to substitute the endostatin sequence taught by O'Reilly *et al.* for the anti-angiogenic sequences taught by Folkman *et al.* because the methods required are conventional techniques routinely used to generate vectors. Further, given the working examples of O'Reilly *et al.* demonstrating that endostatin can be expressed as

functional molecule in various expression systems and the success of Folkman *et al.* for the expression of other anti-angiogenic proteins there would have been a reasonable expectation that an adenoviral vector would be capable of producing an active endostatin when used to infect a cells.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Claim 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman *et al.* (WO 96/35774) and O'Reilly *et al.* (US Patent 5,854,205) as applied to claims 1, 28, 29, 34-37, 39, 40, 41 in further view of Blezinger *et al.*

Folkman *et al.* and O'Reilly *et al.* are summarized above. Briefly, Folkman *et al.* and O'Reilly *et al.* teach that human endothelial cells present in a blood vessel are affected by the anti-angiogenic protein and providing an anti-angiogenic protein to cells prevent angiogenesis (O'Reilly *et al.* figures 8 and 12 and column 2 lines 31-42 and Folkman *et al.* pages 4-5 and 35). Further, both O'Reilly *et al.* and Folkman *et al.* provide expression of the anti-angiogneic proteins by expression vectors which use promoters other than the endogenous anti-angiogenic promoter. Together, O'Reilly *et al.* and Folkman *et al.* make obvious to one having ordinary skill in the art at the time the invention was made to use the adenoviral delivery methods for the delivery of anti-angiogenic factors as disclosed by Folkman *et al.* for the delivery of the specific anti-angiogenic protein endostatin as disclosed by O'Reilly *et al.* Anti-angiogenic proteins are proteins produced and released from cells to affect the surrounding environment of the cell.

O'Reilly *et al.* and Folkman *et al.* teach the affect that anti-angiogenic proteins exert is extracellularly surrounding the cells from which it is secreted, and of all the anti-angiogenic proteins O'Reilly *et al.* specifically teaches that endostatin provides its affect extracellularly and thus, must be secreted if produced by a cell. However, neither O'Reilly *et al.* nor Folkman *et al.* teach to use the heterologous secretion signal peptide sequence of Ig-Kappa when producing anti-angiogenic proteins in cells. Blezinger *et al.* teach that endostatin can be used to inhibit tumor growth. More specifically, Blezinger *et al.* teach a fusion protein comprising endostatin and the Ig-Kappa secretion signal (page 343, middle of second column and summarized in figure 1A). Blezinger *et al.* teach that administration of the polynucleotide encoding the Ig-Kappa-endostatin fusion protein results in the production of endostatin in the serum (results summarized in figure 2). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the polynucleotide sequences encoding the Ig-Kappa-endostatin fusion protein as taught by Blezinger *et al.* in the adenoviral delivery methods for the delivery of anti-angiogenic factors as generally disclosed by Folkman *et al.* and more specifically disclosed by O'Reilly *et al.* for the delivery of the specific anti-angiogenic protein endostatin. One having ordinary skill in the art would have been motivated to use the polynucleotide sequences encoding the Ig-Kappa-endostatin fusion protein as taught by Blezinger *et al.* because of the successful results which demonstrate the production of endostatin in the serum when administered to a subject. There would have been a reasonable expectation of success to use the Ig-Kappa-endostatin fusion protein sequences with those disclosed by O'Reilly *et al.* and

Folkman *et al.* to construct an adenoviral vector comprising a polynucleotide sequence encoding a Ig-Kappa-endostatin fusion protein, and to use said vector to express said protein in a cell.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Claim 1 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman *et al.* (WO 96/35774) and O'Reilly *et al.* (US Patent 5,854,205) as applied to claims 1, 28, 29, 34-37, 40, 41 in further view of Lemarchand *et al.*

Folkman *et al.* and O'Reilly *et al.* are summarized above. Briefly, Folkman *et al.* and O'Reilly *et al.* teach that human endothelial cells present in a blood vessel are affected by the anti-angiogenic protein and providing an anti-angiogenic protein to cells prevent angiogenesis (O'Reilly *et al.* figures 8 and 12 and column 2 lines 31-42 and Folkman *et al.* pages 4-5 and 35). Further, both O'Reilly *et al.* and Folkman *et al.* provide expression of the anti-angiogneic proteins by expression vectors which use promoters other than the endogenous anti-angiogenic promoter. Together, O'Reilly *et al.* and Folkman *et al.* make obvious to one having ordinary skill in the art at the time the invention was made to use the adenoviral delivery methods for the delivery of anti-angiogenic factors as disclosed by Folkman *et al.* for the delivery of the specific anti-angiogenic protein endostatin as disclosed by O'Reilly *et al.* At the time of filing, the RSV promoter was well known and commonly used for the expression of proteins in mammalian cells however, neither O'Reilly *et al.* nor Folkman *et al.* specifically teach to use the RSV promoter in an adenoviral expression system. At the time of filing Lemarchand *et al.* teach to use

recombinant adenoviral vectors for expression transgenes under the control of the RSV promoter, therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the RSV promoter for the expression of anti-angiogenic factors as generally disclosed by Folkman *et al.* and more specifically disclosed by O'Reilly *et al.* for the delivery and expression of the specific anti-angiogenic protein endostatin with an adenoviral expression vector. Again, anti-angiogenic proteins are proteins produced and released from cells to affect the surrounding environment of the cell, and O'Reilly *et al.* and Folkman *et al.* teach the affect that anti-angiogenic proteins exert is extracellularly surrounding the cells from which it is secreted, thus one having ordinary skill in the art would have been motivated to use adenoviral vector system with the RSV promoter as taught by Lemarchand *et al.* because said system was shown to successfully infect cells of the vasculature and that it could be used to express transgenes and produce proteins in said cells. There would have been a reasonable expectation of success to use the adenoviral RSV expression system disclosed by Lemarchand *et al.* for the expression of the endostatin sequence as disclosed by O'Reilly *et al.* and Folkman *et al.* to provide an adenoviral vector comprising an RSV promoter operable linked to a polynucleotide sequence encoding endostatin protein and to use said vector to express said protein in a cell.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Claim 1, 28-30, 33, 38, 45-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman *et al.* (WO 96/35774) and O'Reilly *et al.* (US Patent 5,854,205) as applied to claims 1, 28, 29, 34-37, 39, 40, 41 in further view of Kovesdi *et al.*

Folkman *et al.* and O'Reilly *et al.* are summarized above. Briefly, Folkman *et al.* and O'Reilly *et al.* teach that human endothelial cells present in a blood vessel are affected by the anti-angiogenic protein and providing an anti-angiogenic protein to cells prevent angiogenesis (O'Reilly *et al.* figures 8 and 12 and column 2 lines 31-42 and Folkman *et al.* pages 4-5 and 35). Further, both O'Reilly *et al.* and Folkman *et al.* provide expression of the anti-angiogneic proteins by expression vectors which use promoters other than the endogenous anti-angiogenic promoter. Together, O'Reilly *et al.* and Folkman *et al.* make obvious to one having ordinary skill in the art at the time the invention was made to use the adenoviral delivery methods for the delivery of anti-angiogenic factors as disclosed by Folkman *et al.* for the delivery of the specific anti-angiogenic protein endostatin as disclosed by O'Reilly *et al.* At the time of filing, recombinant adenoviral vectors were well known and commonly used for the expression of proteins in mammalian cells however, neither O'Reilly *et al.* nor Folkman *et al.* specifically teach to use the RSV promoter or an adenoviral promoter to express a transgene or other alterations to the adenoviral vector in the E1-E4 regions. At the time of filing Kovesdi *et al.* teach to use recombinant adenoviral vectors for expression transgenes under the control of the RSV promoter (figure 3) and adenoviral promoters such as the E4 promoter (figure 14), and alterations to the E1-E4 regions to make replication deficient adenoviral vectors. Therefore, it

would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the recombinant adenoviral vectors taught by Kovesdi *et al.* for the expression of anti-angiogenic factors as generally disclosed by Folkman *et al.* and more specifically disclosed by O'Reilly *et al.* for the delivery and expression of the specific anti-angiogenic protein endostatin with an adenoviral expression vector. Moreover, Kovesdi *et al.* specifically uses the A549 cell line as a complementing cell line for propagation of said recombinant adenoviral vectors (see Example 8). At the time of the claimed invention recombinant adenoviral vectors were well known and used to express transgenes in cells, and one having ordinary skill in the art would have been motivated to use adenoviral vectors disclosed by Kovesdi *et al.* with the RSV promoter and adenoviral promoters to express heterologous transgenes because with the deletions the vectors could accommodate larger transgenes (column 7, lines 30-35) and because the resulting vectors are replication defective (column 8, lines 12-44). Recombinant adenoviral vectors were well known and easily manipulated at the time of the claimed invention, and there would have been a reasonable expectation of success to use the recombinant adenoviral vectors disclosed by Kovesdi *et al.* for the expression of the endostatin sequence as disclosed by O'Reilly *et al.* and Folkman *et al.* to provide an adenoviral vector comprising an RSV promoter or adenoviral promoter operable linked to a polynucleotide sequence encoding endostatin protein and to use said vector to express said protein in a cell.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Claim 1, 28, 29, 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Folkman *et al.* (WO 96/35774) and O'Reilly *et al.* (US Patent 5,854,205) in further view of Kovesdi *et al.* as applied to claims 1, 28-30, 33, 38, 45-49 in further view of Henderson *et al.* (US Patent 6,495,130 B1).

Folkman *et al.*, O'Reilly *et al.* and Kovesdi *et al.* are summarized above. Briefly, Folkman *et al.* and O'Reilly *et al.* make obvious to one having ordinary skill in the art at the time the invention was made to use the adenoviral delivery methods for the delivery of anti-angiogenic factors as disclosed by Folkman *et al.* for the delivery of the specific anti-angiogenic protein endostatin as disclosed by O'Reilly *et al.* Kovesdi *et al.* teach specific adenoviral vectors wherein the transgene is under the control of the RSV promoter (figure 3) and adenoviral promoters such as the E4 promoter (figure 14), and alterations to the E1-E4 regions to make replication deficient adenoviral vectors. The additional teachings of Kovesdi *et al.* make obvious the use of said adenoviral vectors for the expression of anti-angiogenic factors as generally disclosed by Folkman *et al.* and more specifically disclosed by O'Reilly *et al.* for the delivery and expression of the specific anti-angiogenic protein endostatin with an adenoviral expression vector. However, neither Folkman *et al.*, O'Reilly *et al.* nor Kovesdi *et al.* teach to use the Hep3B cell line with the adenoviral vector. At the time of filing, recombinant adenoviral vectors were well known and commonly used for the expression of proteins in mammalian cells

and Henderson *et al.* teach to use recombinant adenoviral vectors in Hep3B cells (column 45, starting at line 52). More specifically, Henderson *et al.* teach that recombinant adenoviral vectors deficient in E3 are cytotoxic to Hep3B cells and tumors generated by Hep3B cells. O'Reilly *et al.* and Folkman *et al.* teach to use adenoviral vectors expressing endostatin in methods to decrease the vascularization of tumors for potential methods of treatment of cancer in a subject. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the recombinant adenoviral vectors taught by O'Reilly *et al.* and Folkman *et al.* with those taught by Henderson *et al.* to provide and test a more effective method for treating tumors obtained from Hep3B cells. At the time of the claimed invention recombinant adenoviral vectors were well known and used to express heterologous transgenes in a variety of cell types, and one having ordinary skill in the art would have been motivated to use adenoviral vectors comprising a polynucleotide sequence encoding endostatin protein made obvious by O'Reilly *et al.* and Folkman *et al.* to provide an adenoviral vector and to use said vector to express said protein in Hep3B cells as taught by Henderson *et al.* in order to provide a more effective treatment and/or testing of tumors in model systems. Recombinant adenoviral vectors and their ability to infect a wide variety of cell types was well known at the time of the claimed invention. Therefore, there would have been a reasonable expectation of success to use the recombinant adenoviral vectors that express endostatin made obvious by O'Reilly *et al.* and Folkman *et al.* to infect Hep3B cells in light of the ability of Henderson *et al.*

to infect HepB3 cells with similar recombinant adenoviral vectors which do not express a transgene.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claim is allowed. Claims 42-44 are free of the art of record, however they are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach